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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/667,191
Filing Date: September 15, 2003
Appellant(s): ZHENG ET AL.

Karen Canaan
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed on March 29, 2011 appealing from the Office action mailed November 09, 2010.

(1) Real Party in Interest

The examiner has no comment on the statement, or lack of statement, identifying by name the real party in interest in the brief.

(2) Related Appeals and Interferences

The following are the related appeals, interferences, and judicial proceedings known to the examiner which may be related to, directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal:

The pending claims 1-18 and 26-35 were previously appealed on March 27, 2008 and the BPAI issued a decision reversing Examiner on February 28, 2010. There are no related interferences.

(3) Status of Claims

The following is a list of claims that are rejected and pending in the application:

Claims 1-18 and 26-35 are pending.

Claims 19-25 and 36-39 were withdrawn.

Claims 1-18 and 26-35 are rejected.

(4) Status of Amendments After Final

The examiner has no comment on the appellant's statement of the status of amendments after final rejection contained in the brief.

(5) Summary of Claimed Subject Matter

The examiner has no comment on the summary of claimed subject matter contained in the brief.

(6) Grounds of Rejection to be Reviewed on Appeal

The examiner has no comment on the appellant's statement of the grounds of rejection to be reviewed on appeal. Every ground of rejection set forth in the Office action from which the appeal is taken (as modified by any advisory actions) is being maintained by the examiner except for the grounds of rejection (if any) listed under the subheading "WITHDRAWN

REJECTIONS." New grounds of rejection (if any) are provided under the subheading "NEW GROUNDS OF REJECTION."

(7) Claims Appendix

The examiner has no comment on the copy of the appealed claims contained in the Appendix to the appellant's brief.

(8) Evidence Relied Upon

HONEYMAN K, et al. Development of a snapback method of single-stranded conformation polymorphism analysis for genotyping golden retrievers for the X-linked muscular dystrophy allele. AJVR, Vol. 60, No.6, 1999, pp.734-737.

US 2002/0028455 LAIBINIS et al. 3-2002.

US 6,268,147 BEATTIE et al. 7-2001.

US 5,030,557 HOGAN et al. 7-1991.

SWITZER et al. Enzymatic recognition of the base pair between isocytidine and isoguanidine. Biochemistry, Vol. 32, pp. 10489-10496, 1993.

STRATAGENE CATALOG. Gene characterization kits. Statagene Catalog, pp. 39, 1988.

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

1. Claims 1-5, 9, 10-14, 26 and 32 are rejected under 35 U.S.C. 102(b) as being anticipated by Honeyman et al. (AJVR, 1999, cited in the IDS).

With regard to claims 1 and 32, Honeyman et al. teach a dual-purpose primer for amplifying a target nucleotide sequence in a target molecule, wherein the target molecule has a secondary structure forming region and further wherein the target nucleotide sequence contains a

site of interest proximal to or contained within the secondary structure forming region, wherein the primer comprises:

(a) a primer sequence complementary to a segment of the target nucleotide sequence other than the secondary structure forming region (see p 735 under *Materials and Methods*, where the primer of Honeyman et al. is complementary to the target sequence. See the diagram below where the primer of Honeyman inherently meets all of the functional limitations when the appropriate target is present) and

(b) a blocking sequence substantially complementary to a segment of the secondary structure forming region wherein the blocking sequence disrupts formation of the unwanted secondary structure in an amplicon thereby enabling detection and amplification of the site of interest (see diagram below, where the primer of Honeyman inherently meets all of the functional limitations when the appropriate target is present).

With regard to claim 2, Honeyman et al. teach the site of interest is a nucleic acid sequence (see p 735 under *Materials and Methods*, where the target is canine DNA).

With regard to claim 3, Honeyman et al. teach the site of interest is a single nucleotide polymorphism (see Figure 3, where an adenine residue is replaced by a guanosine residue).

With regard to claim 4, Honeyman et al. teach the primer sequence is complementary to one terminus of the target molecule containing the target nucleotide sequence (see Figure 3).

With regard to claim 5, Honeyman et al. teach further including a nonhybridizing spacer between the primer sequence and the blocking sequence (see Figure 3, where the nonhybridizing sequence is the sequence which anneals back to the normal sequence therefore it does not hybridize with the target sequence carrying the mutation).

With regard to claim 9, Honeyman et al. teach the spacer is nucleotidic (see p. 735 under *Materials and Methods*).

With regard to claim 12, Honeyman et al. teach the spacer is an oligomeric segment comprised of a recurring single nucleotide (see p. 735 under *Materials and Methods*).

With regard to claim 13, Honeyman et al. teach the probe sequence and the spacer are separated from each other by a means for halting transcription there between (see p.735 under *Materials and Methods* and p. 736 col. 2, where the primer sequence is separated from the snap back sequence, which meets the structural limitation recited in the claim because the recitation "by a means for halting transcription there between" is functional language, which is inherently met by the primer of Honeyman).

With regard to claim 14, Honeyman et al. teach the means for halting transcription is an arresting linker (see p.735 under *Materials and Methods* and p. 736 col. 2, where the primer sequence is separated from the snap back sequence which meets the structural limitation recited in the claim because the recitation "an arresting linker" is functional language which is inherently met by the primer of Honeyman).

With regard to claim 26, Honeyman et al. teach an amplicon formed by the action of a DNA polymerase on the primer of claim 1 hybridized to the target nucleotide sequence (s see p.735 under *Materials and Methods*).

*G*C
G C
A T
T A
C G
Target XXXTTCCTTA TCCATAGGCAA

Honeyman's primer CTTAAGGAAT*GATCC*GCATGGG

The underlined nucleotides in Honeyman's primer correspond to clause (a) a primer sequence complementary to a segment of the target nucleotide sequence other than the secondary structure forming region; The nucleotides in italics correspond to the blocking sequence as functionally defined in clause (b) a blocking sequence substantially complementary to a segment of the secondary structure forming region, wherein the blocking sequence disrupts formation of the unwanted secondary structure in an amplicon thereby enabling detection and amplification of the site of interest. When the primer of Honeyman hybridizes to the target the secondary structure of the target will be disrupted and the site in the underlined region will be available for detection or amplification. The primer of Honeyman et al. inherently possesses the functional properties of clause (b) for this particular target.

2. Claims 6-8, 15 and 16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Honeyman et al. (AJVR, 1999, cited in the IDS) in view of Laibinis et al. (US 2002/0028455).

The teachings of Honeyman et al. are discussed above.

Honeyman et al. do not teach all the limitations of claims 6-8, 15 and 16.

Laibinis et al. teach the spacer is non-nucleotidic (see paragraph 0014), the spacer is comprised of a synthetic hydrophilic oligomer (see paragraph 0014, where the linker is comprised of chains of alkylene units, specifically polyethylene gylcol, making it hydrophilic) and the spacer is comprised of about 3 to about 50 alkylene oxide units selected from ethylene oxide and combinations of ethylene oxide and propylene oxide (see paragraph 0014).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use the Primer, as taught by Honeyman et al. with the concept of varying

the linkers as taught by Laibinis et al. Laibinis et al. teach a variety of linkers can be used in a primer molecule. A skilled artisan would readily understand from reading Laibinis et al. that type and lengths of linkers can be successfully varied. An ordinary practitioner would have been motivated to use the Primer, as taught by Honeyman et al. with the concept of varying the linkers as taught by Laibinis et al. in order to successfully choose a linker for a primer.

3. Claims 10-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Honeyman et al. (AJVR, 1999, cited in the IDS) in view of Switzer et al. (Biochemistry, 1993).

The teachings of Honeyman et al. are discussed above. Honeyman et al. do not teach all the limitations of claims 10-11.

Switzer et al. teach the non-natural nucleotides of iso-G and iso-C in a primer molecule (see the abstract and Figure 3).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use the Primer, as taught by Honeyman et al. with the concept of non natural nucleotides as taught by Switzer et al. Switzer et al. teach non natural nucleotides can be incorporated into a template using the Klenow fragment of DNA polymerase. Additionally, Switzer et al. teach non natural bases are useful in a laboratory setting. A skilled artisan would readily understand from reading Switzer et al. that the non natural nucleotides of iso-C and iso-G can be successfully used in primer oligonucleotides. An ordinary practitioner would have been motivated to use the Primer, as taught by Honeyman et al. with the concept of non natural nucleotides as taught by Switzer et al. Switzer et al. in order to increase specificity of the oligonucleotide for a target. The invention was made to combine the dual purpose primer for amplification as taught by Honeyman et al. into a kit format as discussed by Stratagene catalog

since the Stratagene catalog teaches a motivation for combining reagents of use in an assay into a kit, "Each kit provides two services: 1) a variety of different reagents have been assembled and pre-mixed specifically for a defined set of experiments. Thus one need not purchase gram quantities of 10 different reagents, each of which is needed in only microgram amounts, when beginning a series of experiments. When one considers all of the unused chemicals that typically accumulate in weighing rooms, desiccators, and freezers, one quickly realizes that it is actually far more expensive for a small number of users to prepare most buffer solutions from the basic reagents. Stratagene provides only the quantities you will actually need, premixed and tested. In actuality, the kit format saves money and resources for everyone by dramatically reducing waste. 2). The other service provided in a kit is quality control" (page 39, column 1).

4. Claims 1and 32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hogan et al. (USPN 5,030,557).

Hogan et al. teach using a combination of a primer and a “helper” sequence in which the “helper” sequence acts functionally to block intramolecular secondary hairpin target formation to facilitate PCR of the target regions (see col. 4). While Hogan et al. do not teach the primer and helper are combined in a single sequence as instantly claimed. However one of ordinary skill in the art would have been motivated to combine the two sequences of Hogan et al. into a single sequence as instantly claimed because primer design is routine and obvious to a skilled artisan. A skilled artisan would recognize there are two ways to combine the sequences of Hogan et al.; with a linking sequence or directly as a single contiguous sequence. A skilled artisan would have been motivated to combine the two sequences of Hogan et al. into a single primer sequence

because a single sequence results in a lower cost assay which is less labor intensive and more practical.

(10) Response to Argument

Introduction

The independent claims 1 is drawn to a dual-purpose primer for amplifying a target nucleotide sequence in a target molecule comprising a secondary structure forming region and a site of interest proximal to or contained within the secondary structure forming region and a primer comprising a sequence complementary to a segment of the target sequence other than the secondary structure forming region, a blocking sequence complementary to a segment of the secondary structure forming region. The independent claim 32 is drawn to a hybridization probe comprising said complementary sequence to the target molecule and a blocking sequence complementary to a segment of the secondary structure forming region. The dependent claims are further drawn to limit the independent claims.

Anticipation

The anticipation is based upon Honeyman et al. reference. Honeyman et al. teach a primer and a probe comprising a complementary sequence to a target nucleic acid sequence and a blocking sequence complementary to a secondary structure forming region of the target sequence proximal to a site of interest in the target molecule.

On page 7-18 of the appeal brief, the Appellants' assert that Honeyman et al. does not teach the primer/probe as claimed in the instant independent claims 1 and 32 and provide comparison of the primer of the instant specification with that of the primers taught by Honeyman et al. The assertions were found unpersuasive for the following reasons. First, the claims recite in

alternative that the target nucleotide sequence comprises a site of interest proximal to *or* within the secondary structure forming region. Thus the assertions drawn to the site of interest within the secondary structure region are unpersuasive. Second, the instant independent claims 1 and 32 broadly recite the structure of the primer / probe and the primer/probe structure taught by Honeyman et al. do not exclude the broader scope of the claims since the instant claims are not restricted to the cited primer of the specification because the instant claims do not necessarily read on said primer sequence of the instant specification. Third, as stated in MPEP 2145 Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See In re Van Geuns, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Accordingly the limitations upon which the arguments depend are not present in the claims, that is, the primer/probe sequence limitations are not present in the claims. Fourth, as discussed in the rejection, Honeyman et al. teach a primer/probe comprising the structural limitations as required by the instant claims and the assertions drawn to specific sequences of primer /probe were found unpersuasive since the broader scope of the claims are not restricted to the sequences of primer/probes, instead the claims require a target sequence with a site of interest, a secondary structure forming region and a blocking sequence and the reference of Honeyman et al. teach said limitations as discussed in the rejection.

With regard to the Appellants' arguments on page 19-24, the arguments were found unpersuasive. First the arguments drawn to primer complementary to one terminus of the target molecule, the arguments were found unpersuasive because Honeyman et al teaches that the primers flank a site of interest (mutant allele), which clearly teach that at least one terminus is hybridized closer to or proximal to the site of interest in the target sequence. Further the claims

as presented do not recite a target terminus, instead the claims recite that the primer is complementary to a segment of the target nucleotide sequence and the flanking region of Honeyman et al. reference read on the target segment as claimed. With regard to the arguments drawn to a non-hybridizing spacer, the arguments were found unpersuasive because as discussed in the rejection the loop portion of the snapback portion represents a spacer region and the loop portion does not hybridize to any part of the target sequence and the Fig. 3 shows the loop region showing single stranded sequence that is not hybridized back to the target segment (bottom panel of fig. 3). With regard to means-plus function, the arguments were fully considered, however, as discussed in the rejection the cited portions of Honeyman et al. teach that the reduction in the amplification efficiency of the normal product is attributable to the formation of hairpin structure because of the presence of a mutant allele, which indicates that the transcription is arrested because of the mutant nucleotide which is considered as linker.

On page 23-24, the Appellants argue that the claim interpretation is based on the target and not on the primer as claimed and the claim interpretation mandates earlier Board decision on appeal. The assertions are found unpersuasive because any nucleic acid primer /probe structure necessarily depends on the target sequence and the said primer /probe is designed with an intention to detect the target sequence or a site of interest (mutation) in a target. Thus the claim interpretation based on the target is not ignoring the claim limitations or mandating the Board decision.

Prima Facie Obviousness

The prima facie obviousness rejection is based on five independent rejections: Honeyman et al. in view of Laibinis et al.; Honeyman et al. in view of Switzer et al.; Honeyman et al. in view of Beattie et al.; Honeyman et al. in view of Stratagene Catalog. and in view of Hogan et al.

The Appellants arguments on the page 24-35 were fully considered and found unpersuasive.

First, as discussed above, Honeyman et al. teach the limitations in the independent claims 1, 32 and as discussed in the rejection it is obvious to modify the teachings of Honeyman et al. in a manner of Laibinis et al., Switzer et al., Beattie et al. and Stratagene Catalog to render the dependent claims obvious.

With reference to the Appellants arguments drawn to the Hogan et al. reference, the arguments were found unpersuasive because as discussed in the rejection it is obvious to modify the probe and helper probe sequences to derive at the primer sequence as claimed, since the oligonucleotide probe sequences with foldings (hairpin structure formation) taught by Hogan et al. were designed based on the target sequence binding regions, which forms the basis for the primer design. Accordingly it is obvious to modify the teachings of Hogan et al. to achieve at the primer/probe limitations as claimed.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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